2. The method for treatment and prevention of dental caries of claim 1 wherein the chimeric monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing the chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

3. The method for treatment and prevention of dental caries of claim 2 wherein step c further comprises synthesis of a nucleic acid construct comprising:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

6. The method for treatment and prevention of dental caries of claim 1 wherein the mammal to be treated is human, and the other species is mouse.

7. A method for treatment and prevention of dental caries in a mammal comprising administration to a subject in need of such treatment a chimeric monoclonal antibody that specifically binds to a cariogenic organism and elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal.

8. The method for treatment and prevention of dental caries of claim 7 wherein the monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with the cariogenic organism;

b) identifying a hybridoma from the mammalian host that secrete a monoclonal antibody specific to the antigen displayed by the cariogenic organism; and

c) preparing a chimeric monoclonal antibody comprising a complementarity-determining region from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

9. The method for treatment and prevention of dental caries of claim 8 wherein the step c further comprises preparation of a nucleic acid construct that includes:

a) a nucleic acid sequence that codes on expression for the complementarity determining region of the monoclonal antibody; and

b) a nucleic acid sequence that codes on expression for the constant domain of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

12. The method for treatment and prevention of dental caries of claim 8, wherein the mammalian host is a mouse, and the mammal to be treated is a human.

II. REMARKS

This amendment is responsive to the first Office Action mailed February 11, 2002, in connection with the above-identified patent application. Applicants wish to thank Examiner Zeman for the helpful and courteous interview extended to the undersigned attorney and to Dr. Shi, one of the inventors. The present invention was explained. Arguments of Section 102 and

103 rejections were addressed and the above amendments were discussed. Reconsideration of the application in view of the amendments and the following remarks is respectfully requested.

Claims 1-4, 6-10, 12 and 17 are pending. For the Examiner's convenience, a copy of the claims as they will stand upon entry of the present amendments (as indicated) is attached hereto as Exhibit A.

A, Regarding the Priority Claim

The Office Action acknowledges a claim for domestic priority under 35 U.S.C. §119(e) to a provisional application. Applicants respectfully disagree and point out that applicants have not given proper instructions to enter such priority claim for the record.

B. Regarding the Amendments

Claims 1 and 2 have been amended to replace the phrase "monoclonal antibody" with "chimeric monoclonal antibody". Claims 1-4 and 6-9 have also been amended to correct antecedent basis and clerical or grammatical errors. These amendments are supported by the specification and do not add any new matter. Entering of these amendments is respectfully requested.

Claims 5, 11 and 13-16 have been canceled. Applicants respectfully submit that the cancellation of these claims is without prejudice and solely for the purpose of expediting prosecution. Applicants hereby expressly reserve the right to prosecute these claims at a different time.

C. Rejections under 35 U.S.C. § 112

The Office Action rejects claims 5, 11 and 13-16 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. In order to expedite prosecution, applicants have canceled claims 5, 11 and 13-16 without prejudice and expressly reserve the right to pursue these claims at a different time.

Withdrawal of the rejection of claims 5, 11 and 13-16 under 35 U.S.C. § 112, first paragraph is respectfully requested.

The rejection of claims 3 and 9 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite is respectfully traversed.

The Office Action states that the phrase "step of preparing" is vague and indefinite. Applicants respectfully submit that the phrase "step of preparing" clearly refers to step c) of "preparing the monoclonal antibody" in the antecedent claim. Nevertheless, in order to expedite the prosecution of the present invention claims 3 and 9 have been amended to replace the phrase "the step of preparing" with "step c)" as suggested by the Examiner.

Withdrawal of the rejection of claims 3 and 9 under 35 U.S.C. §112, second paragraph is respectfully requested.

D. Rejections under 35 U.S.C. § 102

The rejection of claims 1, 6 and 7 under 35 U.S.C. § 102(b), as allegedly being anticipated by Lehner (U.S. Patent No. 5,352,446) is respectfully traversed.

Applicants respectfully point out that claims 1, 6 and 7 as amended recite a "chimeric monoclonal antibody", which is different from the murine monoclonal antibody disclosed in Lehner. Therefore, Lehner does not anticipate the present invention.

Withdrawal of the rejection of claims 1, 6 and 7 under 35 U.S.C. § 102(b) is respectfully requested.

E. Rejections under 35 U.S.C. § 103

The rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. § 103, as allegedly being obvious over Ma et al. (European Journal of Immunology 1994, Vol. 24 (1) pages 131-138, "Ma") in view of Adair et al (U.S. Patent No. 5,877,293, "Adair") is respectfully traversed.

The present invention is directed to a method of treating and preventing dental caries by oral administration of a chimeric antibody that specifically binds to a cariogenic organism and elicits a humoral immune response. The reference cited by the Office Action, *i.e.*, Ma reference does not teach or suggest the present invention. On the contrary, Ma teaches away from the methods taught by the present invention.

Specifically Ma uses an approach different from the approach taught by the present invention. According to Ma, dental caries may be prevented by using antibodies to block the

surface of *S. mutans,* cause bacterial aggregation, thus prevent colonization of *S. mutans* on dental surfaces. In contrast, the present invention teaches that dental caries can be prevented by using antibodies to induce a humoral immune response to *S. mutans*, e.g., eliminate *S. mutans* through a humoral immune response.

According to Ma's approach, the antibodies used by Ma was specifically modified to increase the prevention of bacteria colonization with the believe that the Fc-mediated humoral response is not essential. (See Ma at page 131, second and third paragraphs and at page 136, last paragraph). In particular, the modification was directed to replacing the Fc portion of the IgG with the Fc portion of the IgA, with the understanding that IgA is more effective than IgG in preventing bacterial colonization. (See Ma et al., at page 131, third paragraph). This modification strategy gives minimum consideration, if any, to the induction of a humoral immune response since an IgG would have been a better choice than IgA in terms of eliciting a humoral immune response. In fact, Ma deems the modified antibody effective based on its function of causing cell clumping and despite its inability to affect *S. mutans* rate of growth. (See Ma at page 136). Ma, in essence, suggests that prevention of colonization is key while antibody mediated humoral immune response is dispensable, which teaches away from the method provided by the present invention.

In light of Ma's disclosure, it is not obvious to one skilled in the art that he or she could treat or prevent dental caries by using a method different from Ma's, *e.g.,* the method provided by the present invention. Ma's disclosure does not teach or suggest using the antibody to elicit a humoral immune response. On the contrary, Ma's disclosure and the references cited in Ma all strongly suggest that Fc-mediated immune response, *e.g,* cytotoxicity via complement or cell-mediated pathway is not essential in treating or preventing dental caries. In the absence of any specific teaching, one skilled in the art would not have been motivated to divert away from Ma's method and approach, *e.g.,* it is not obvious to replace antibodies effective in blocking the surface of *S. mutans* with antibodies effective in inducing a humoral immune response to kill *S. mutans.*

Even if one skilled in the art has decided to experiment with humoral immune responses in treating or preventing dental caries, he or she would not have had any reasonable expectation of success. It is well known in the art that mucosal surfaces contain limited immune components, especially lack IgG and IgM antibodies that are required to

activate antibody-dependent cell-mediated cytotoxicity or complement-dependent cytolysis. Therefore, it would have been uncertain prior to the present invention whether introducing a functional Fc by a chimeric antibody would have triggered a humoral immune response from the oral immune-apparatus that normally does not produce a humoral immune response.

In summary, Ma's disclosure does not teach or suggest the present invention. Ma promotes and focus on an approach that is different from what is used by the present invention. In fact, Ma effectively teaches away from the methods taught by the present invention.

Adair is cited as a secondary reference. Adair discloses the making of a humanized antibody against carcinoembryonic antigen (CEA). Adair does not cure the deficiency of Ma because it too fails to teach or suggest using chimeric antibodies to treat dental caries, especially by eliciting a humoral immune response.

In summary, the present invention is not obvious over Ma in view of Adair. Withdrawal of the rejection of claims 1-4, 6-10, 12 and 17 under 35 U.S.C. §103 is respectfully requested.

In view of the amendment and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 07-1895.

Respectfully submitted,

Date: 5/6/02

Nan Wu, M.D., Ph.D.
Reg. No. 43,360
Telephone: 415-836-2531
Facsimile: 415-836-2501

GRAY CARY WARE & FREIDENRICH LLP
153 Townsend Street, Suite 800
San Francisco, California 94107

Enclosures: Exhibit A

EXHIBIT A

CLAIMS UPON ENTRY OF THE AMENDMENT

1. (Amended) A method for the treatment and prevention of dental caries in a mammal comprising oral administration of a chimeric monoclonal antibody that specifically binds to a cariogenic organism[,] and [which] elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal, wherein the portion of the monoclonal antibody that binds to the cariogenic organism is derived from a species other than that [the] of the mammal to be treated.

2. (Amended) The method for treatment and prevention of dental caries of claim 1 wherein the chimeric monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with [at least one] the cariogenic organism;

b) identifying a hybridoma [hybridomas] from the mammalian host that secrete a monoclonal antibody [antibodies] specific to the antigen displayed by the [surface antigens of at least one] cariogenic organism; and

c) preparing [a] the chimeric monoclonal antibody comprising a complementarity-determining region [regions] from the monoclonal antibody of step b) above and a constant domain from the mammal to be treated.

3. (Amended) The method for treatment and prevention of dental caries of claim 2 wherein [step of preparing] step c further comprises synthesis of a nucleic acid construct comprising:

a) a nucleic acid sequence that codes on expression for [a] the complementarity determining region of the monoclonal antibody [secreted by the hybridomas derived from the mammalian host of claim 2 above]; and

b) a nucleic acid sequence that codes on expression for [a] the constant domain [region] of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

4. The method for treatment and prevention of dental caries of claim 3 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 3 above.

5. (Cancelled) The method for treatment and prevention of dental caries in a mammal of claim 4, wherein the monoclonal antibody is administered by oral ingestion of tissue from a eukaryotic host transformed with the nucleic acid construct of claim 4 above.

6. (Amended) The method for treatment and prevention of dental caries of claim 1 wherein the mammal to be treated is [man] human, and the other species is mouse.

7. (Amended) A method for treatment and prevention of dental caries in a mammal comprising administration to a subject in need of such treatment [of] a chimeric monoclonal antibody that specifically binds to a cariogenic organism and [which] elicits a humoral immune response to an antigen displayed by the cariogenic organism from the mammal.

8. The method for treatment and prevention of dental caries of claim 7 wherein the monoclonal antibody is produced by the steps of:

a) inoculating a mammalian host with [at least one] the cariogenic organism;

b) identifying a hybridoma [hybridomas] from the mammalian host that secrete a monoclonal antibody [antibodies] specific to the antigen displayed by the [surface antigens of at least one] cariogenic organism; and

c) preparing a chimeric monoclonal antibody comprising a complementarity-determining region [regions] from the monoclonal antibody of step b) above and a constant domain from [a] the mammal to be treated.

9. (Amended) The method for treatment and prevention of dental caries of claim 8 wherein [step of preparing] the step c further comprises preparation of [at least one] a nucleic acid construct that includes:

a) a nucleic acid sequence that codes on expression for [a] the complementarity determining region of the monoclonal antibody [secreted by the hybridomas derived from the mammalian host of claim 2 above]; and

b) a nucleic acid sequence that codes on expression for [a] the constant domain [region] of an antibody selected from the group consisting of class IgG and class IgM of the mammal to be treated.

10. The method for treatment and prevention of dental caries of claim 9 wherein the chimeric monoclonal antibody is expressed by a eukaryotic host that has been transformed with the nucleic acid construct of claim 9 above.

11. (Cancelled) The method for treatment and prevention of dental caries in a mammal of claim 9, wherein the monoclonal antibody is administered by oral ingestion of tissue from a eukaryotic host that has been transformed with the nucleic acid construct of claim 9 above.

12. The method for treatment and prevention of dental caries of claim 8, wherein the mammalian host is a mouse, and the mammal to be treated is [man] a human.

13. (Cancelled) The method for treatment and prevention of dental caries of claim 5 wherein the eukaryote is a plant.

14. (Cancelled) The method for treatment and prevention of dental caries of claim 5 wherein the eukaryote is a plant of the species *Brassica*.

15. (Cancelled) The method for treatment and prevention of dental caries of claim 11 wherein the eukaryote is a plant.

16. (Cancelled) The method for treatment and prevention of dental caries of 5 claim 11 where the eukaryote is a plant of the species *Brassica*.

17. The method for treatment and prevention of dental caries of claim 8, wherein the mammal to be treated is a dog or a cat.